

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>PG3749</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 00/ 07669</b>	International filing date (day/month/year) <b>08/08/2000</b>	(Earliest) Priority Date (day/month/year) <b>10/08/1999</b>
Applicant <b>GLAXO GROUP LIMITED</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of **6** sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
  - contained in the international application in written form.
  - filed together with the international application in computer readable form.
  - furnished subsequently to this Authority in written form.
  - furnished subsequently to this Authority in computer readable form.
  - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  Certain claims were found unsearchable (See Box I).

3.  Unity of invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

USE OF EP4 RECEPTOR LIGANDS IN THE TREATMENT OF NEUROPATHIC PAIN AND COLON CANCER

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

**INTERNATIONAL SEARCH REPORT**International application No.  
PCT/EP 00/07669**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,3-4 (partially), 5,7,9-10,12-13 (partially), 14,16,18

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,3-4 (partially),5,7,9-10,12-13 (partially),14,16, 18

Use of ep4 ligands for treating neuropathic pain.

2. Claims: 2,3-4(partially),6,8,11,12-13(partially),15,17

Use of ep4 ligands for treating colon cancer.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 3.

Although claims 5,14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Further defect(s) under Article 17(2)(a):

Continuation of Box 3.

Present claims 1,3-5,7-10,12-14,16-18 relate to a compound defined by reference to a desirable characteristic or property, namely the capacity of binding the receptor EP4, as a ligand or antagonist.

Present claims 4,18 relate to compounds defined by reference to a desirable characteristic or property, namely the activity as COX-2 inhibitors, as 5-lipoxygenase inhibitors, as NSAID, as leukotriene receptor antagonists, as DMARD, as adenosine 1 agonists, as recombinant human TNF receptor fusion protein, as sodium channel antagonist, as NMDA antagonists and as 5HT1 agonists.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds prepared in examples at pages 15-19.

Claims searched completely: none.

Claims searched incompletely: 1,3-5,7-10,12-14,16-18.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

International Application No

EP 00/07669

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 A61K31/4035 A61P29/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE, SCISEARCH

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 330 307 A (GLAXO GROUP LTD) 21 April 1999 (1999-04-21) page 1, line 1 - line 31 --- US 4 327 092 A (COLLINGTON ERIC W ET AL) 27 April 1982 (1982-04-27) page 1, paragraph 1 - paragraph 3 column 2, paragraph 49 - paragraph 57 --- EP 0 520 573 A (GLAXO INC) 30 December 1992 (1992-12-30)  page 3; figure II ---	7,9,16, 18  7,9,16, 18  1,3-5,7, 9,10, 12-14, 16,18  -/-
A		

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## ° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

6 March 2001

Date of mailing of the international search report

16.07.01

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Bonzano, C

## INTERNATIONAL SEARCH REPORT

International Application No

EP 00/07669

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 501 579 A (MERCK FROSST CANADA INC) 2 September 1992 (1992-09-02)  page 5, line 66 -page 6, line 13 page 4; figure 1 ---	1,3-5,7, 9,10, 12-14, 16,18
A	US 5 834 463 A (KATO KOICHI ET AL) 10 November 1998 (1998-11-10)  example 75 column 1, paragraph 7 -----	1,3-5,7, 9,10, 12-14, 16,18

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

EP 00/07669

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
GB 2330307	A	21-04-1999	NONE	
US 4327092	A	27-04-1982	AT 191781 A AU 540147 B AU 6995781 A BE 888645 A CA 1173830 A CH 646965 A DE 3117087 A DK 189881 A EP 0078609 A ES 501740 D ES 8207498 A ES 510838 D ES 8303386 A FI 811350 A,B, FR 2481703 A GB 2075503 A,B IE 51241 B IL 62734 A IT 1170929 B JP 1704052 C JP 3014028 B JP 57018671 A JP 1638962 C JP 2063054 B JP 58082723 A KR 8500214 B NL 8102116 A NO 811470 A NZ 196966 A PH 16854 A PT 72951 A,B SE 8102731 A US 4342756 A US 4427614 A ZA 8102838 A	15-11-1985 01-11-1984 05-11-1981 30-10-1981 04-09-1984 28-12-1984 11-03-1982 31-10-1981 11-05-1983 16-09-1982 16-12-1982 01-02-1983 01-05-1983 31-10-1981 06-11-1981 18-11-1981 12-11-1986 31-10-1985 03-06-1987 14-10-1992 25-02-1991 30-01-1982 31-01-1992 27-12-1990 18-05-1983 06-03-1985 16-11-1981 02-11-1981 31-05-1984 19-03-1984 01-05-1981 21-12-1981 03-08-1982 24-01-1984 28-04-1982
EP 0520573	A	30-12-1992	AU 1864092 A CA 2072551 A FI 922964 A IE 922083 A JP 6025284 A MX 9203643 A NO 922530 A US 5252560 A ZA 9204758 A	07-01-1993 28-12-1992 28-12-1992 30-12-1992 01-02-1994 31-01-1995 28-12-1992 12-10-1993 24-02-1993
EP 0501579	A	02-09-1992	CA 2061716 A JP 5140143 A US 5227399 A	29-08-1992 08-06-1993 13-07-1993
US 5834463	A	10-11-1998	AU 2352495 A CA 2189053 A EP 0757681 A WO 9529900 A JP 8208627 A JP 10500402 T	29-11-1995 09-11-1995 12-02-1997 09-11-1995 13-08-1996 13-01-1998

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:  
**GLAXO WELLCOME PLC**  
 Glaxo Wellcome House  
 Attn. LANE, Graham  
 Berkeley Avenue  
 Greenford  
 Middlesex UB6 0NN  
 UNITED KINGDOM

Corporate Intellectual Property		THE INTERNATIONAL SEARCH REPORT	
RECEIVED		INIT	20 JUL 2001
18 JUL 2001			<i>CW</i>
Action Date	ATTN	FILE	<i>TC</i>

**PCT**

GlaxoSmithKline  
 NOTIFICATION OF TRANSMISSION OF  
 THE INTERNATIONAL SEARCH REPORT  
 OR THE DECLARATION

20 JUL 2001

(PCT Rule 44.1)  
 Received NFSP

Date of mailing  
 (day/month/year)

16/07/2001

Applicant's or agent's file reference  <b>PG3749</b>	FOR FURTHER ACTION      See paragraphs 1 and 4 below
International application No.  <b>PCT/ EP 00/ 07669</b>	International filing date  (day/month/year) <b>08/08/2000</b>
Applicant  <b>GLAXO GROUP LIMITED</b>	

1.  The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the      International Bureau of WIPO  
 34, chemin des Colombettes  
 1211 Geneva 20, Switzerland  
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2.  The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3.  **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

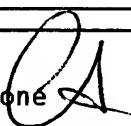
no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority   European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Claudia Aragone 
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## NOTE TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

**When?** Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

**How?** Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

**The amendments must be made in the language in which the international application is to be published.**

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

**The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.**

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

**The following examples illustrate the manner in which amendments must be explained in the accompanying letter:**

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the International application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PCTENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 06 juillet 2001 (06.07.01)
Applicant's or agent's file reference PG3749
International application No. PCT/EP00/07669

## From the INTERNATIONAL BUREAU

To:

LANE, Graham  
 GlaxoSmithKline  
 Corporate Intellectual Property  
 Two New Horizons Court  
 Brentford  
 Middlesex TW8 9EP  
 ROYAUME-UNI

## IMPORTANT NOTIFICATION

International filing date (day/month/year)  
 08 août 2000 (08.08.00)

1. The following indications appeared on record concerning: <input type="checkbox"/> the applicant <input type="checkbox"/> the inventor <input checked="" type="checkbox"/> the agent <input type="checkbox"/> the common representative				
Name and Address LANE, Graham Glaxo Wellcome plc Glaxo Wellcome House Berkeley Avenue Greenford Middlesex UB6 0NN United Kingdom	State of Nationality		State of Residence	
	Telephone No.		020 8966 8000	
	Facsimile No.		020 8966 8838	
	Teleprinter No.			
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: <input type="checkbox"/> the person <input type="checkbox"/> the name <input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence				
Name and Address LANE, Graham GlaxoSmithKline Corporate Intellectual Property Two New Horizons Court Brentford Middlesex TW8 9EP United Kingdom	State of Nationality		State of Residence	
	Telephone No.		020 8966 8412	
	Facsimile No.		020 8966 8838	
	Teleprinter No.			
3. Further observations, if necessary:				
4. A copy of this notification has been sent to: <input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the designated Offices concerned <input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the elected Offices concerned <input checked="" type="checkbox"/> the International Preliminary Examining Authority <input type="checkbox"/> other:				

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  S. Buttay  Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 14 February 2002 (14.02.02)
Applicant's or agent's file reference PG3749
International application No. PCT/EP00/07669

From the INTERNATIONAL BUREAU

To:

LANE, Graham  
 GlaxoSmithKline  
 Corporate Intellectual Property  
 (CN9.25.1)  
 980 Great West Road  
 Brentford  
 Middlesex TW8 9GS  
 ROYAUME-UNI

## IMPORTANT NOTIFICATION

International filing date (day/month/year)  
 08 August 2000 (08.08.00)

1. The following indications appeared on record concerning: <input type="checkbox"/> the applicant <input type="checkbox"/> the inventor <input checked="" type="checkbox"/> the agent <input type="checkbox"/> the common representative				
Name and Address  LANE, Graham GlaxoSmithKline Corporate Intellectual Property Two New Horizons Court Brentford Middlesex TW8 9EP United Kingdom	State of Nationality		State of Residence	
	Telephone No. 020 8966 8412			
	Facsimile No. 020 8966 8838			
	Teleprinter No.			
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: <input type="checkbox"/> the person <input type="checkbox"/> the name <input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence				
Name and Address  LANE, Graham GlaxoSmithKline Corporate Intellectual Property (CN9.25.1) 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom	State of Nationality		State of Residence	
	Telephone No. 44 20 8047 5000			
	Facsimile No. 44 20 8047 6894			
	Teleprinter No.			
3. Further observations, if necessary:				
4. A copy of this notification has been sent to: <input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the designated Offices concerned <input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> the International Preliminary Examining Authority <input type="checkbox"/> other:				

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Sean Taylor  Telephone No.: (41-22) 338.83.38
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## PENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

Date of mailing (day/month/year) 09 April 2001 (09.04.01)	To:  Commissioner US Department of Commerce United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2/5C24 Arlington, VA 22202 ETATS-UNIS D'AMERIQUE  in its capacity as elected Office
International application No. PCT/EP00/07669	Applicant's or agent's file reference PG3749
International filing date (day/month/year) 08 August 2000 (08.08.00)	Priority date (day/month/year) 10 August 1999 (10.08.99)
Applicant CLAYTON, Nicholas, Maughan et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

09 February 2001 (09.02.01)

in a notice effecting later election filed with the International Bureau on:

\_\_\_\_\_

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Pascal Piriou  Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

## (PCT Article 36 and Rule 70)

Applicant's or agent's file reference PG3749	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP00/07669	International filing date (day/month/year) 08/08/2000	Priority date (day/month/year) 10/08/1999	
International Patent Classification (IPC) or national classification and IPC A61K31/00			
Applicant GLAXO GROUP LIMITED			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I     Basis of the report
- II     Priority
- III     Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV     Lack of unity of invention
- V     Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI     Certain documents cited
- VII     Certain defects in the international application
- VIII     Certain observations on the international application

Date of submission of the demand 09/02/2001	Date of completion of this report 07.12.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Pa I Soto, R Telephone No. +49 89 2399 7346



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/07669

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-19                   as originally filed

**Claims, No.:**

1-18                   as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description,               pages:
- the claims,                   Nos.:
- the drawings,               sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/07669

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

**6. Additional observations, if necessary:**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
  - the entire international application.
  - claims Nos. 2, 3-4 (in part), 6, 8, 11, 12-13 (in part), 15 and 17; 5 and 14 (industrial applicability); .

because:

- the said international application, or the said claims Nos. 5 and 14 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. 2, 3-4 (in part), 6, 8, 11, 12-13 (in part), 15 and 17.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
  - the written form has not been furnished or does not comply with the standard.
  - the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes: Claims 1, 3-5, 9-10, 12-14 and 18
	No: Claims 7 and 16
Inventive step (IS)	Yes: Claims 1, 3-5, 8, 10 and 12-14
	No: Claims 7, 9, 16 and 18

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/07669

Industrial applicability (IA) Yes: Claims 1-4, 6-13 and 15-18; for 5 and 14 see separate sheet  
No: Claims

2. Citations and explanations  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/07669

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. No International Preliminary Examination will be carried out in respect of subject-matter which is not covered by the International Search Report (see Rule 66.1(e) PCT), i.e. in respect of **claims 2, 3-4** (as dependent on claim 2), **6, 8, 11, 12-13** (as dependent on claim 11), **15 and 17**.
2. **Claims 5 and 14** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

3. Reference is made to the following documents:

**D1:** GB-A-2 330 307 (GLAXO GROUP LTD) 21 April 1999 (1999-04-21)  
**D2:** US-A-4 327 092 (COLLINGTON ERIC W ET AL) 27 April 1982 (1982-04-27)

4. The present application relates to the use of an EP4 receptor ligand or receptor in the manufacture of a medicament for the treatment of neuropathic pain (**claims 1 and 10**), a method of treating neuropathic pain in a mammal comprising the administration of an EP4 receptor ligand (**claim 5 and 14**), and a pharmaceutical composition comprising an EP4 receptor ligand (**claims 7, 9, 16 and 18**).
5. The present application does not meet the requirements of the PCT with respect to novelty (Art. 33(2)) for the following reasons.
  - (a) Both **D1** (see lines 1-31 on page 1) and **D2** (see paragraphs 1-3 on column 1 and lines 49-57 on column 2) disclose pharmaceutical compositions comprising EP4

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/07669

receptor ligands and are therefore **novelty destroying for present claims 7 and 16.**

- (b) The following should be noted in relation to the present opinion concerning novelty of the claims. The technical feature of "for use in the treatment of neuropathic pain" in present claims 7 and 16 does not render the subject-matter novel over **D1** and **D2**. This is because said claims are directed to a pharmaceutical preparation and a pharmaceutical preparation is defined by its components and not by the medical indication intended for it.
- (c) Furthermore, all those documents cited in the application (see lines 16-22 on page 2) disclose therapeutic indications for the corresponding compounds. For the same reason all these prior art documents are also novelty destroying for present claims 7 and 16.

6. Present claims 9 and 18 appear to be novel over the prior art. However said claims do not involve an inventive step (Art. 33(3) PCT) for the following reasons.

**D1** and **D2**, both of which can be regarded as the closest prior art, disclose pharmaceutical compositions containing an EP4 receptor ligand which are useful to treat various conditions. The difference between these disclosures and the subject-matter of present claims 9 and 18 is that in the pharmaceutical compositions according to said claims a COX-2 inhibitor is present. This technical feature could only render the subject-matter inventive if it provides an unexpected effect or property (for example, a synergistic effect) to the corresponding pharmaceutical compositions. However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of claims 9 and 18.

7. Present **claims 1, 3-5, 10, 12-14 and 17-18** appear to satisfy the requirements of the PCT with respect to novelty and inventive step (Art. 33(2) and (3)), because none of the prior art documents disclose or suggests that EP4 receptor ligands or antagonists can be useful for the treatment of neuropathic pain.

8.1. **Claims 7, 9, 16 and 18** meet the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/07669

8.2. For the assessment of the present **claims 1, 3-5, 10 and 12-14** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment (present claims 5 and 14), but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**PCT REQUEST**

Original (for SUBMISSION) - printed on 04.08.2000 02:51:11 PM

<b>0</b>	<b>For receiving Office use only</b>	
<b>0-1</b>	International Application No.	
<b>0-2</b>	International Filing Date	
<b>0-3</b>	Name of receiving Office and "PCT International Application"	
<b>0-4</b>	<b>Form - PCT/RO/101 PCT Request</b>	
<b>0-4-1</b>	Prepared using	<b>PCT-EASY Version 2.91 (updated 01.07.2000)</b>
<b>0-5</b>	<b>Petition</b> The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
<b>0-6</b>	Receiving Office (specified by the applicant)	<b>European Patent Office (EPO) (RO/EP)</b>
<b>0-7</b>	Applicant's or agent's file reference	<b>PG3749</b>
<b>I</b>	Title of invention	<b>USE OF EP4 RECEPTOR LIGANDS IN THE TREATMENT OF, INTER ALIA, NEUROPATHIC PAIN AND COLON CANCER</b>
<b>II</b>	<b>Applicant</b>	
<b>II-1</b>	This person is:	<b>applicant only</b>
<b>II-2</b>	Applicant for	<b>all designated States except US</b>
<b>II-4</b>	Name	<b>GLAXO GROUP LIMITED</b>
<b>II-5</b>	Address:	<b>Glaxo Wellcome House Berkeley Avenue Greenford, Middlesex UB6 0NN United Kingdom</b>
<b>II-6</b>	State of nationality	<b>GB</b>
<b>II-7</b>	State of residence	<b>GB</b>
<b>II-8</b>	Telephone No.	<b>020 8966 8000</b>
<b>II-9</b>	Facsimile No.	<b>020 8966 8838</b>
<b>III-1</b>	<b>Applicant and/or inventor</b>	
<b>III-1-1</b>	This person is:	<b>applicant and inventor</b>
<b>III-1-2</b>	Applicant for	<b>US only</b>
<b>III-1-4</b>	Name (LAST, First)	<b>CLAYTON, Nicholas, Maughan</b>
<b>III-1-5</b>	Address:	<b>Glaxo Wellcome plc Gunnels Wood Road Stevenage, Hertfordshire SG1 2NY United Kingdom</b>
<b>III-1-6</b>	State of nationality	<b>GB</b>
<b>III-1-7</b>	State of residence	<b>GB</b>

**PCT REQUEST**

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III-2	<b>Applicant and/or inventor</b>	
III-2-1	This person is:	<b>applicant and inventor</b>
III-2-2	Applicant for	<b>US only</b>
III-2-4	Name (LAST, First)	<b>COLLINS, Susanne, Denise</b>
III-2-5	Address:	<b>Glaxo Wellcome plc Gunnels Wood Road Stevenage, Hertfordshire SG1 2NY United Kingdom</b>
III-2-6	State of nationality	<b>GB</b>
III-2-7	State of residence	<b>GB</b>
III-3	<b>Applicant and/or inventor</b>	
III-3-1	This person is:	<b>applicant and inventor</b>
III-3-2	Applicant for	<b>US only</b>
III-3-4	Name (LAST, First)	<b>FOORD, Steven, Michael</b>
III-3-5	Address:	<b>Glaxo Wellcome plc Gunnels Wood Road Stevenage, Hertfordshire SG1 2NY United Kingdom</b>
III-3-6	State of nationality	<b>GB</b>
III-3-7	State of residence	<b>GB</b>
III-4	<b>Applicant and/or inventor</b>	
III-4-1	This person is:	<b>applicant and inventor</b>
III-4-2	Applicant for	<b>US only</b>
III-4-4	Name (LAST, First)	<b>GIBLIN, Gerard, Martin, Paul</b>
III-4-5	Address:	<b>Glaxo Wellcome plc Gunnels Wood Road Stevenage, Hertfordshire SG1 2NY United Kingdom</b>
III-4-6	State of nationality	<b>GB</b>
III-4-7	State of residence	<b>GB</b>
IV-1	<b>Agent or common representative; or address for correspondence</b>  The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	<b>agent</b>
IV-1-1	Name (LAST, First)	<b>LANE, Graham</b>
IV-1-2	Address:	<b>Glaxo Wellcome plc Glaxo Wellcome House Berkeley Avenue Greenford, Middlesex UB6 0NN United Kingdom</b>
IV-1-3	Telephone No.	<b>020 8966 8000</b>
IV-1-4	Facsimile No.	<b>020 8966 8838</b>

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V	<b>Designation of States</b>	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	<b>AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT</b> <b>EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT</b> <b>EP: AT BE CH&amp;LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT</b> <b>OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT</b>
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	<b>AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&amp;LI CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW</b>
V-5	<b>Precautionary Designation Statement</b> In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	<b>Exclusion(s) from precautionary designations</b>	<b>NONE</b>
VI-1	<b>Priority claim of earlier national application</b>	
VI-1-1	Filing date	<b>10 August 1999 (10.08.1999)</b>
VI-1-2	Number	<b>9918745.2</b>
VI-1-3	Country	<b>GB</b>
VI-2	<b>Priority claim of earlier national application</b>	
VI-2-1	Filing date	<b>01 December 1999 (01.12.1999)</b>
VI-2-2	Number	<b>9928437.4</b>
VI-2-3	Country	<b>GB</b>
VII-1	<b>International Searching Authority Chosen</b>	<b>European Patent Office (EPO) (ISA/EP)</b>

**PCT REQUEST**

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VIII	Check list	number of sheets	electronic file(s) attached
VIII-1	Request	4	-
VIII-2	Description	19	-
VIII-3	Claims	3	-
VIII-4	Abstract	1	pg3749abstract.txt
VIII-5	Drawings	0	-
VIII-7	TOTAL	27	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-12	Priority document(s)	Item(s) VI-1, VI-2	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	Figure of the drawings which should accompany the abstract		
VIII-19	Language of filing of the international application	English	
IX-1	Signature of applicant or agent		
IX-1-1	Name (LAST, First)	LANE, Graham	

**FOR RECEIVING OFFICE USE ONLY**

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported International application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

**FOR INTERNATIONAL BUREAU USE ONLY**

11-1	Date of receipt of the record copy by the International Bureau	
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**PCT (ANNEX - FEE CALCULATION SHEET)**

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PG3749

(This sheet is not part of and does not count as a sheet of the international application)

<b>0</b>	<b>For receiving Office use only</b>			
0-1	International Application No.			
0-2	Date stamp of the receiving Office			
<b>0-4</b>	<b>Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet</b>			
0-4-1	Prepared using	<b>PCT-EASY Version 2.91 (updated 01.07.2000)</b>		
<b>0-9</b>	<b>Applicant's or agent's file reference</b>	<b>PG3749</b>		
<b>2</b>	<b>Applicant</b>	<b>GLAXO GROUP LIMITED, et al.</b>		
<b>12</b>	<b>Calculation of prescribed fees</b>	<b>fee amount/multiplier</b>	<b>total amounts (EUR)</b>	
12-1	Transmittal fee	T	⇒	<b>102</b>
12-2	Search fee	S	⇒	<b>945</b>
12-3	International fee Basic fee (first 30 sheets)	b1		<b>409</b>
12-4	Remaining sheets	0		
12-5	Additional amount (X)	9		
12-6	Total additional amount	b2		<b>0</b>
12-7	b1 + b2 =	B		<b>409</b>
12-8	Designation fees Number of designations contained in international application	87		
12-9	Number of designation fees payable (maximum 8)	8		
12-10	Amount of designation fee (X)	88		
12-11	Total designation fees	D		<b>704</b>
12-12	PCT-EASY fee reduction	R		<b>-126</b>
12-13	Total International fee (B+D-R)	I	⇒	<b>987</b>
<b>12-17</b>	<b>TOTAL FEES PAYABLE (T+S+I+P)</b>		⇒	<b>2,034</b>
<b>12-19</b>	<b>Mode of payment</b>	<b>authorization to charge deposit account</b>		
<b>12-20</b>	<b>Deposit account instructions</b> The receiving Office:	<b>European Patent Office (EPO) (RO/EP)</b>		
12-20-1	is hereby authorized to charge the total fees indicated above to my deposit account	✓		
12-20-2	is hereby authorized to charge any deficiency or credit any over-payment in the total fees indicated above to my deposit account	✓		
12-20-3	is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account	✓		
<b>12-21</b>	Deposit account No.	<b>28050185</b>		
<b>12-22</b>	Date	<b>04 August 2000 (04.08.2000)</b>		

**PCT (ANNEX - FEE CALCULATION SHEET)**

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PG3749

<b>12-23</b>	Name and signature	LANE, Graham 
--------------	--------------------	--

**VALIDATION LOG AND REMARKS**

<b>13-1-1</b>	Applicant remarks Annotate	The Abstract may contain Greek characters
<b>13-2-6</b>	Validation messages Contents	Yellow! The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
		Green? The international application contains no drawings. Please verify.
<b>13-2-7</b>	Validation messages Fees	Green? Please confirm that fee schedule utilized is the latest available
<b>13-2-8</b>	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.
<b>13-2-9</b>	Validation messages Annotate	Green? All indications that can be made on the Request form are specifically provided for by the software. Please confirm validity of additional indication.

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

**RECEIVED**

To:  
LANE, Graham  
LANE, Graham  
GlaxoSmithKline  
Corporate Intellectual Property  
Two New Horizons Court  
Middlesex TW8 9EP  
GRANDE BRETAGNE

11 DEC 2001

NEW HORIZONS COURT

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Action Date	ATTN
PCT 2 DEC 2001	
FILE	

**NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

(PCT Rule 71.1)

Date of mailing  
(day/month/year) 07.12.2001

Applicant's or agent's file reference

PG3749

**IMPORTANT NOTIFICATION**

International application No.  
PCT/EP00/07669

International filing date (day/month/year)  
08/08/2000

Priority date (day/month/year)  
10/08/1999

Applicant  
GLAXO GROUP LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

**4. REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer

Hundt, D

Tel. +49 89 2399-8042



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number  
**WO 01/10426 A2**

(51) International Patent Classification<sup>7</sup>: **A61K 31/00**

(21) International Application Number: **PCT/EP00/07669**

(22) International Filing Date: 8 August 2000 (08.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
9918745.2 10 August 1999 (10.08.1999) GB  
9928437.4 1 December 1999 (01.12.1999) GB

(71) Applicant (*for all designated States except US*): **GLAXO GROUP LIMITED [GB/GB]**; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **CLAYTON, Nicholas, Maughan [GB/GB]**; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **COLLINS, Susanne, Denise [GB/GB]**; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **FOORD, Steven, Michael [GB/GB]**; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). **GIBLIN, Gerard, Martin, Paul**

[GB/GB]; Glaxo Wellcome plc, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: **LANE, Graham**; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— *Without international search report and to be republished upon receipt of that report.*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**WO 01/10426 A2**

(54) Title: USE OF EP4 RECEPTOR LIGANDS IN THE TREATMENT OF, INTER ALIA, NEUROPATHIC PAIN AND COLON CANCER

(57) Abstract: The present invention relates to the use of an EP4 receptor ligand in the manufacture of a medicament for use in the treatment of neuropathic pain, colon cancer, migraine, and for increasing the latency of HIV infection.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
15 February 2001 (15.02.2001)

PCT

(10) International Publication Number  
**WO 01/10426 A3**

(51) International Patent Classification<sup>7</sup>: **A61K 31/4035, A61P 29/02**

(21) International Application Number: **PCT/EP00/07669**

(22) International Filing Date: **8 August 2000 (08.08.2000)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:  
9918745.2 10 August 1999 (10.08.1999) GB  
9928437.4 1 December 1999 (01.12.1999) GB

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(81) Designated States (*national*): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.**

(84) Designated States (*regional*): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).**

Published:

— *with international search report*

(88) Date of publication of the international search report:  
**20 December 2001**

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**WO 01/10426 A3**

(54) Title: **USE OF EP4 RECEPTOR LIGANDS IN THE TREATMENT OF NEUROPATHIC PAIN AND COLON CANCER**

(57) Abstract: **The present invention relates to the use of an EP4 receptor ligand in the manufacture of a medicament for use in the treatment of neuropathic pain, colon cancer, migraine, and for increasing the latency of HIV infection.**

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/07669

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 A61K31/4035 A61P29/02

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE, SCISEARCH

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 330 307 A (GLAXO GROUP LTD) 21 April 1999 (1999-04-21) page 1, line 1 - line 31 ---	7,9,16, 18
X	US 4 327 092 A (COLLINGTON ERIC W ET AL) 27 April 1982 (1982-04-27) page 1, paragraph 1 - paragraph 3 column 2, paragraph 49 - paragraph 57 ---	7,9,16, 18
A	EP 0 520 573 A (GLAXO INC) 30 December 1992 (1992-12-30)  page 3; figure II ---	1,3-5,7, 9,10, 12-14, 16,18  -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

6 March 2001

Date of mailing of the international search report

16.07.01

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Bonzano, C

**INTERNATIONAL SEARCH REPORT**

International Application No

PCT/EP 00/07669

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 501 579 A (MERCK FROSST CANADA INC) 2 September 1992 (1992-09-02)  page 5, line 66 -page 6, line 13 page 4; figure 1 ---	1,3-5,7, 9,10, 12-14, 16,18
A	US 5 834 463 A (KATO KOICHI ET AL) 10 November 1998 (1998-11-10)  example 75 column 1, paragraph 7 -----	1,3-5,7, 9,10, 12-14, 16,18

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 00/07669

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,3-4 (partially), 5,7,9-10,12-13 (partially), 14,16,18

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,3-4 (partially),5,7,9-10,12-13 (partially),14,16, 18

Use of ep4 ligands for treating neuropathic pain.

2. Claims: 2,3-4(partially),6,8,11,12-13(partially),15,17

Use of ep4 ligands for treating colon cancer.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 3.

Although claims 5,14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Further defect(s) under Article 17(2)(a):

Continuation of Box 3.

Present claims 1,3-5,7-10,12-14,16-18 relate to a compound defined by reference to a desirable characteristic or property, namely the capacity of binding the receptor EP4, as a ligand or antagonist. Present claims 4,18 relate to compounds defined by reference to a desirable characteristic or property, namely the activity as COX-2 inhibitors, as 5-lipoxygenase inhibitors, as NSAID, as leukotriene receptor antagonists, as DMARD, as adenosine 1 agonists, as recombinant human TNF receptor fusion protein, as sodium channel antagonist, as NMDA antagonists and as 5HT1 agonists.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds prepared in examples at pages 15-19.

Claims searched completely: none.

Claims searched incompletely: 1,3-5,7-10,12-14,16-18.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/07669

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